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Selecting container closure components with confidence: A data-driven approach to Container Closure Integrity

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There are few signs that momentum in the biologics market is set to slow down. Strong pipeline growth and a dominant share of drug approvals by the US Food & Drug Administration (FDA) in recent years points to the sector's sustained potential for years to come.

Bringing a new drug to market can undoubtedly deliver great rewards for patients and patent-holders alike, but whether in the case of biologics or small molecules, it is an undertaking that also carries well-documented risks.

With development costs typically in the billions of dollars[1], an average timeframe of ten years between first patent filing and market availability[2], and only an estimated 10% of drugs in clinical trials receiving regulatory approval[3], the pathway to return on investment is far from straightforward. In order to get there as quickly as possible, companies must blend agility, knowledge and resources in the right combination to meet development deadlines and answer the demands of regulatory agencies.

One major potential point of friction on this approval journey is the need to specify and verify a compatible packaging combination for your drug product. Container closure integrity (CCI) is a critical aspect of drug development, and one that demands attention and investment early in the process to avoid complications and possible harm further down the line. This point is underlined by FDA data, which reveals that around a third (34%) of injectable product recalls in recent years can be linked to particulates or a lack of sterility attributable to the container closure combination.[4]

Containment issues during the development phase can also prove costly, with reworking of the system resulting in delays and additional costs. For resource-limited emerging companies, which are the major driving force behind innovation in the biologics market, such challenges add to the already high burden they face in achieving regulatory approval. Indeed, such companies take an average of two years longer to get to market compared with their more established counterparts and, since 2019, they have also consistently received Complete Response Letters (CRLs) at a higher rate.[5]

Particularly in the case of emerging companies then, containment can be seen as a key concern. Failure to manage the issue effectively within the development phase has the potential to derail pre-approval progress, while it also has the potential to become a major disrupting factor following regulatory approval if containment failings trigger a product recall. In this whitepaper, we discuss how West is supporting pharmaceutical partners in this critical area through an efficient, data-driven process that employs innovative methods to accelerate the selection of a closure containment system that meets the requirements of the modern regulatory landscape.

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[1] Based on data from Tufts Center for the Study of Drug Development
[2] Emerging Biopharma's Contribution to Innovation, June 2022, IQVIA
[3] Biotechnology Innovation Organization: Clinical Development Success Rates
[4] https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls (Accessed July 31, 2023) and https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/recalls-biologics (Accessed July 31, 2023)
[5] Emerging Biopharma's Contribution to Innovation, June 2022, IQVIA

The changing challenge of containment

There is little doubt that drug containment has become a more complex undertaking in recent years. The days are gone when a vial, stopper and seal might have been specified independently and then combined into a unified system. A combination of advances in materials science, modern manufacturing technologies and more stringent requirements from regulatory authorities puts us in a position today where drug containment is thankfully far more advanced and, as a result, recognisably better.

In recent years, regulators and standard setting organizations have published an increasing number of documents governing various aspects of containment with a view to continually improving the conditions under which a drug is packaged. Ultimately, these changes are introduced under the dual overarching ambitions of maintaining drug efficacy and enhancing patient safety. An example is the addition of USP <1207> in 2017, which goes into 40 pages of detail on the different measurement methods for container closure integrity (CCI). Another example is USP <382>, which was published in 2018 as an entirely new chapter and covers many more tests than the known functionality tests relating to fragmentation, self-sealing and penetrability for vials and cartridge seals included within USP <381>.

Today, this has been extended into a 13-page document that essentially covers the functional suitability of all elastomer components in the context of parenteral product packaging and delivery systems, with a scope that encompasses everything from bottles, vials and syringes to blow-fill-seal (BFS) containers and infusion bags.

Aside from the clear drive for improved quality, a key takeaway is that the focus of regulatory thinking is gravitating away from components in isolation and towards a more systems-level view. When considering the specific potential risk presented by endotoxins, particles or leachables, for example, it makes logical sense for pharmaceutical and biopharmaceutical companies to address these issues from a patient perspective, reflecting on how such issues might manifest themselves within the drug delivery systems that patients will themselves experience in real-world situations.

At a deeper level, regulators have also raised expectations around the rationale behind drug containment choices. Here, there is an expectation for strategies to be validated not just by rhetoric but by extensive dossiers of facts, evidence and data. This can be seen in the revised EU GMP Annex I on the manufacture of sterile medicinal products, which comes into force in August 2023 and stipulates the requirement for a documented Contamination Control Strategy (CCS) and an integrity-testing regime linked to "knowledge and experience of the container and closure systems being used". Furthermore, USP <1207> talks of how the integrity of the final packaged product is directly influenced by the "critical dimensional tolerances" of each component, their material properties, how they are assembled, and how they combine to form the closed package.

With this shift towards a data-driven, systems-view of drug containment, it is important to zero-in on the specific parameters that can influence the performance of components in combination, and to test them in a way that mirrors the context of real-world performance. For example, fragmentation test data for a stopper based on a 28-gauge needle might demonstrate technical compliance, but this evidence holds less validity if it is to be used with a spike in the final system. Furthermore, the risk of delamination, which is a process of the interaction between drug product and vial, cannot be gauged through assessment of the vial alone.

Selecting the right combination of container-closure elements from all the available choices on the market can therefore be seen to be a challenging and complex task. Aspects such as dimensional fit are clearly critical, but there are many other tests to be conducted and many more levels of data to be gathered to demonstrate, document and verify CCI. Confidently arriving at a final decision demands both time and resources, but these are factors that can impact on costs and impair time-to-market, which can in turn compromise a drug product's commercial potential.

At West, we are in an ideal position to address this challenge, bringing together experience of container closure systems with extensive knowledge of regulatory requirements. We have combined this expertise into a three-stage process to support companies embarking on such a decision, with a clear aim to introduce greater levels of efficiency, saving precious development time while also meeting the highest levels of compliance with the very latest regulatory standards.

Three-stage selection process

The first step in any such process is to conduct a paper-based theoretical assessment of the specified components. This stage will incorporate testing of Interference Fit and Stack-Up analysis to narrow down a large number of potential candidate components into a more selective number of compatible options. At the end of the theoretical assessment, modelling approaches are then used to arrive at a shortlist capable of advancing to the final third stage where component choices are tested for CCI to assess their suitability.

The use of modelling and simulation in the second step of the component selection process is a critical factor in accelerating development time and securing important cost savings. These benefits are down to the fact that analysis is carried out within highly accurate virtual environments that replicate real-world scenarios. This avoids the resource- and time-intensive methods associated with more traditional pathways, where extensive iterations to prototypes are required to assess and control performance variables. It is important to note that analysis to identify optimisation of fit between components should be carried out before a system can progress to testing, since the purpose of the final step is to verify choices whose validity has already been deemed satisfactory.

Modelling might be considered a relatively novel approach, but it is one supported by regulators across the world. In the US, the FDA has a model-informed drug development program designed to "accelerate access to safe and effective products"[6]. The European Medicines Agency (EMA) has also endorsed this approach, as demonstrated through its Modelling and Simulation Working Party. Echoing the language of the FDA, the EMA describes this approach as a "powerful tool"[7] in facilitating the regulatory assessment of medicines.

[6] https://www.fda.gov/drugs/news-events-human-drugs/cder-conversation-model-informed-drug-development#:~:text=Model%2Dinformed%20drug%20development%20(MIDD,drug%20development%20and%20decision%2Dmaking. (accessed July 31, 2023)
[7] https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/methodology-working-party (accessed July 31, 2023)

To explain more about how modelling works in practice, here we provide an example of the three-stage process in action, reflecting on how this process supports the validation of the chosen components at each point. In the example we will discuss here, the system is comprised of a European blowback type Corning® Valor® glass vial in conjunction with a West NovaPure® stopper and a West Flip-Off® CCS seal. Dimensions for all elements are based on the according ISO 8362 standards.

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Theoretical Assessment:
- Interference Fit
- Stack-Up

Modeling Approach:
- FEA Analysis
- CT Scan
- DeltaCube

Experimental Verification:
- CCI Testing

Flip-Off® CCS Seals
5417, RU Gamma

NovaPure® Stopper
1358 Serum,
4023/50 RU Steam

Valor® Glass Vial
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Stage 1 Theoretical Assessment

In the theoretical assessment stage, the first task is to prove dimensional compatibility. This can be achieved through an assessment of Interference Fit, which gauges the interface between stopper and vial based on the physical dimensions for each component. The values for these dimensions are drawn from the technical specification of the components and, as such, there is acknowledgement that the precise fit will vary marginally according to manufacturing tolerances in both vial and stopper. The extent of this theoretical variance, and therefore the dimensional compatibility of the components, is reflected in the Interference Fit (IF) range, which is calculated using reference measurements for the vial neck and the stopper diameter.

In this particular example, the stopper plug has an outer diameter of 7.45mm (±0.15mm), and the vial neck has an inner diameter of 7.0mm (±0.2mm). Using the maximum and minimum possible measurements within these tolerances will elicit a low-end IF figure at one extreme where the smallest plug diameter is employed in conjunction with the largest vial neck inner diameter. Conversely, there will also be an upper-end or high IF figure where the largest plug diameter is used in conjunction with the smallest vial neck diameter. Within this range, components that conform to the typical dimensional specification provide a nominal IF figure, which can be regarded as the expected norm. Here, the variances result in a nominal IF of 6%, which sits squarely in the middle of the generally accepted industry standard Interference Fit range of between 2% and 10%, proving that the components deliver a strong dimensional fit.

The next aspect of dimensional compatibility to be assessed is how much of the seal skirt will be left to be crimped under the seal crown. This can be understood by performing Stack-Up Analysis, which is calculated by combining measurements for the height of the vial crown and the height of the stopper flange when seated in the vial. This total figure is then subtracted from the total length of the seal skirt to reveal the seal-skirt overhang length (SSOL), which will dictate how much excess will be crimped under the crown.

The SSOL will, again, not be an absolute figure because of minor component-to-component variations. As such, the analysis will result in a spectrum of values that allow us to arrive at a nominal, mid-range figure. It is also important to note that the analysis assumes that the rubber is exposed to a compression percentage of 35%, which is based on typical measurements from real-world fill-finish operations. In this example, the nominal SSOL is calculated to be 1.24mm, which sits within the estimated industry range of 0.76mm to 1.3mm. Having therefore proved dimensional compatibility between components, the process can move to the second stage where further analysis can be carried out using modelling techniques.

Stage 2 Modelling Approaches

There are three approaches employed here: Finite Element Analysis; computerised tomography (CT) scanning; and DeltaCube™, a modelling platform developed by West to accelerate the Stack-up Analysis already discussed above.

The first of these, Finite Element Analysis (FEA), is a method typically used in structural engineering applications within the built environment to evaluate how the various forces acting on a specific material, such as pressure or temperature, affect its physical properties. It is based on the principle of dividing complex shapes into finite elements, which are then subjected to desired impacts to reveal the physical parameters at play.

Here, the parameters analysed for the vial, stopper and seal were: the coefficient of thermal expansion (CTE), which tells us how much shrinkage or expansion occurs when materials are heated and cooled; Young's Modulus, which is related to a material's stiffness and reveals how much stretching and deformation occurs when tensile stress is applied; and Poisson's Ratio, which tells us how the materials' physical properties change on the plane that is perpendicular to the applied force. All of these differential calculations were carried out at low, medium and high levels of compression, with the two-dimensional axisymmetric model providing a close-up visualisation of the chosen closure combination.

The decisive area for maintaining CCI is the land seal, and maximum contact pressure between the vial and the stopper at low compression was recorded at 0.91 MPa and around 1.4 MPa at high compression. The model revealed that force was evenly distributed with no gaps observed between the surfaces. It also highlighted how much more of the seal is crimped underneath the vial neck under higher compression forces. Overall, the results are seen to be consistent with a secure seal.

In the next step, the closure combination was subject to a CT scan, which echoed the findings of the FEA model and underlined the fact that higher pressure correlates to more compression of the rubber and, therefore, the seal being crimped further under the rim. It also confirmed there were no visible gaps between the vial and the rubber surface.

The final step in the Modelling Approaches stage is to subject the chosen components to DeltaCube™ modelling platform analysis. This modelling platform uses actual dimensions for vial, stopper and seal as inputs rather than taking measurements from technical drawings, as was the case for the Stack-Up Analysis in the previous stage. It also allows for the compression percentage on the stopper to be defined along with minimum and maximum acceptable values for seal-skirt length, with acknowledgement of the fact that both over-crimped and under-crimped vials can be markers of poor CCI.

With inputs and parameters established, the DeltaCube™ modelling platform calculates the probability distribution of over-crimping and under-crimping, referred to in terms of P. This is based on the percentage of possible stack-up combinations that fall outside the desired seal-skirt overhang length (SSOL) range according to the specified compression level and the supplied dimensional data. In our example, at low compression of 15%, the results are at the low end of the acceptable range and the overhang length with the highest probability of occurrence is 0.7mm. At high compression of 45%, the results sit in the middle of the range and the overhang length with the highest probability of occurrence is around 1.3mm. In both compression modes, therefore, P tends towards zero, further indicating strong dimensional fit and allowing the chosen combination to progress to the final testing stage.

Stage 3 Experimental Verification

With confidence in dimensional fit provided by theoretical analysis and modelling approaches, helium leak testing can be applied to assess the closure system's CCI. In this case, the study was conducted at low, medium and high compression for non-stored samples at ambient temperature. In addition, to test CCI over time, samples under medium compression were evaluated after accelerated ageing of 6 months, 12 months and 24 months under elevated temperature, and also after 6 months of real-time ageing under ambient temperature. All samples fell well below the Kirsch limit of low probability for microbial ingress and can, therefore, be considered to safely maintain integrity under a range of storage conditions.

Data-rich approach to validating closure choices

On reaching the end of this three-stage process, we are able to reflect on the fact that the chosen components – Valor® glass vial, NovaPure® stopper, and Flip-Off® CCS seal – together form a secure closure combination. This conclusion is evidenced by extensive data, including theoretical assessment of Interference Fit and Stack-Up; confirmation of dimensional fit using the modelling approaches of Finite Element Analysis (FEA), CT scanning and DeltaCube™ modelling platform calculations; and CCI validation through helium leak testing.

Furthermore, these methods have allowed such a conclusion to be reached in an accelerated timeframe by employing efficient methods. This not only minimises direct testing costs, but it also contributes to a reduction in overall development costs and supports companies in their efforts of getting to market as quickly as possible with a patient-safe containment system available from a single source of supply.

With speed of operational deployment in mind, West can introduce further efficiencies by making components available in Ready Pack™, a ready-to-use sterile containment solution that smooths the pathway to fill-finish operations, removing the need for additional sterilisation processes. We also understand the importance of supporting companies in their scale-up journey, which is why components can be supplied in quantities that support both early-stage pilots and commercial scale production.

If you would like to learn more about product options and service offerings available in support of selecting packaging components for your drug, visit the West Ready Pack™ Containment System and the Delta Cube™ pages or Contact Us so that we can connect you with an account manager in your region.

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